

S. Sgouros
A. V. Kulkarni
S. Constantini

The international infant hydrocephalus study: concept and rationale

Received: 12 May 2005
Published online: 15 October 2005
© Springer-Verlag 2005

S. Sgouros
Birmingham Children's Hospital,
Birmingham, UK

A. V. Kulkarni
Hospital for Sick Children,
Toronto, Canada

S. Constantini (✉)
Department Pediatric Neurosurgery,
Dana Children's Hospital,
Tel Aviv Sourasky Medical Center,
6 Weizman Street,
Tel Aviv, 64239, Israel
e-mail: sconsts@netvision.net.il
Tel.: +972-3-6974686
Fax: +972-3-6973451

Abstract *Introduction:* During the recent meetings of the International Study Group on Neuroendoscopy and the International Society for Pediatric Neurosurgery, the consensus view emerged that there is a need to assess the value and efficacy of neuroendoscopic procedures against shunting in a scientific manner, to resolve long-lasting debates on the subject.

Material and methods: A prospective randomized, controlled trial of endoscopic third ventriculostomy vs shunting in children presenting under the age of 2 years with pure aqueduct stenosis is being proposed and organized (the International Infant Hydrocephalus Study, IIHS). The participating surgeons must adhere to the philosophy of randomization and be suitably experienced in endoscopic techniques in infants. The primary outcome of the trial will be the overall health-related quality of life of these children at 5 years of age. Hence, the study is focusing on the effect of surgery on neurodevelopment, rather than the less important issue of shunt or stoma survival, that has been debated extensively with no conclu-

sion so far. Intention-to-treat analysis will be performed according to the first surgery. Secondary outcomes such as complication and reoperation rate, total hospitalization time and cost, need for repeat imaging, and others will be analyzed as well. *Results:* Pure aqueduct stenosis is relatively rare, making recruitment problematic, but has been chosen to avoid other confounding factors that could influence outcome. More than 25 centers worldwide have committed already to patient recruitment to the study. It is anticipated that recruitment will last for 2 years, aiming for 91 patients per arm. The study has started recruiting patients already in some countries. *Conclusion:* It is hoped that the trial will not only provide answers to unsettled debates on the value of neuroendoscopy but also create a network of collaborating pediatric neurosurgeons for future initiatives.

Keywords Infantile hydrocephalus · Ventricular shunt · Endoscopic third ventriculostomy · Neuroendoscopy · Clinical trials

Introduction

Neuroendoscopy has enjoyed a renewed interest in the last decade. While it is not new as a technique—it has been used

as early as the beginning of the 20th century by Walter Dandy and other pioneers—technological advancements have made it safer and easier, making endoscopic treatment of hydrocephalus feasible even in neonates and newborns.

Even after the initial enthusiasm and renewed interest has settled and consolidated, endoscopic third ventriculostomy (ETV) for treatment of obstructive hydrocephalus is considered now as first line of management for many patients. For many neurosurgeons who are strong advocates of endoscopy, it is considered unethical not to offer the option of ETV as the treatment of choice in children with obstructive hydrocephalus due to aqueduct stenosis, over the age of 1–2 years (Kulkarni 2005 unpublished data) [5, 9, 11, 16, 23, 33, 56]. Its effectiveness has been demonstrated also in hydrocephalus, resulting from many other causes such as Chiari or Dandy-Walker malformations, myelomeningocele, brain tumors, and NPH, even in situations complicated by a history of hemorrhage, infection, or previous ETV attempts, as well as in cases of shunt malfunction [3, 5, 8–11, 17–19, 28, 29, 34–39, 50–52, 55, 59]. While in older children, the indications for endoscopic treatment have been well defined, much debate has centered in recent years on the value of this treatment in the first few months of life. While different success results have emerged from clinical studies, inevitably, all these studies outline the lack of consensus on the value of third ventriculostomy in infants and neonates. This has led effectively to the organization of the International Infant Hydrocephalus Study (IIHS).

Shunt vs ETV in infants with aqueduct stenosis: debate on the merits of the two treatment types

While there have been more than 30 recent studies that address the question of choice of treatment for hydrocephalus in infants, no consensus opinion has emerged. Standards of inclusion criteria, treatment choices, and outcome measures are inconsistent among studies. Multiple single institution studies with small numbers of patients have produced data of debatable statistical validity. Nonstandardized inclusion criteria have resulted in studies with heterogeneous samples, which may include full-term or premature infants, with simple or complex noncommunicating hydrocephalus, with or without a previous history of shunting, infection, or hemorrhage, and/or patients with myelomeningocele, and/or various forms of communicating hydrocephalus. These heterogeneous samples make valid comparisons virtually impossible, since many current studies suggest that the single most significant factor in the success of an ETV is the etiology of the hydrocephalus [1, 4, 9, 10, 25, 41].

In addition to the problems of inconsistent inclusion standards and small numbers, there is inconsistency in the definition of *success* and *failure* among studies making meaningful comparisons impossible. The only criterion for success used in most studies has been some variation on freedom from shunt dependency. Even that single criterion is not applied consistently, with some studies insisting on total shunt freedom after a single ETV attempt, others including shunt freedom after a repeat ETV as well, and in

most cases, there are short-term follow-ups that do not define or address the risks of delayed failure. Relying on the single criterion of shunt freedom completely ignores equally important outcomes such as neurodevelopmental and quality of life, hospitalization time, number of surgeries, and economic issues as well. Neurodevelopmental impact is an especially significant factor for infants diagnosed with hydrocephalus, given the known pattern of cognitive and neuropsychological issues associated with shunted hydrocephalic children. This typically includes a pattern of lower IQ scores, hyperverbosity (cocktail party syndrome), deficits in working memory, and problems with attention, planning, organization, and self-monitoring (executive functioning) [13, 22, 23, 44, 53, 60].

Table 1 shows a consolidated comparison of results from various important studies, focusing on success rates of ETV in the first 2 years of life. A wide variation of success has been reported. Critical review of these studies highlights some of their limitations.

Beems and Grotenhuis [4] concluded that etiology rather than age is the significant factor in the success or failure of ETV. However, there is no detailed analysis by patient age, partly due to the fact that the numbers were too small for statistical significance, and they make no attempt to assess neurodevelopment or functional quality of life. Burn et al. [6] broke down their data by age, etiology, and complications. However, their numbers were too small to be statistically meaningful. Nevertheless, they concluded that ETV is not worth attempting in patients with intraventricular hemorrhage (IVH) who are under 1 year old but is still worth considering in patients with other diagnoses. They commented also on the relatively high incidence of subsequent shunt infection after failed ETV (4 of the 13 patients). Buxton et al., in two similar publications, analyzed a general group of infants under 1 year of age [7] and also focused on a group of premature infants [8]. The numbers in each group are small, and they cannot be combined due to the greater rate of complications and problems in the premature group. They concluded that in anatomically suitable patients, ETV is worth trying, as it does not significantly add to the morbidity, it involves little or no mortality, and it can be unpredictably successful in a patient group with a high proportion of shunt complications. They argued in favor of the presumed reduction in morbidity, mortality, and economic burden compared with shunting. However, they acknowledged that the true long-term benefit of such procedures cannot be shown until a randomized, controlled trial comparing shunt against ETV is completed. Cinalli et al. [10] emphasized the need for a definitive study before any conclusions can be reached. They stated that before ETV can be widely accepted as the treatment of choice for these patients, a detailed long-term follow-up study is required. Genitori et al. [15] attempted a larger-scale study, which, unfortunately, did not include an analysis of outcome by age. Hopf et al. [20], in another large study, included only four infants under 1 year old, with multiple

Table 1 Synopsis of reported success rate of ETV in published series of the last 15 years

Author	Number of patients	Result of ETV
Beems and Grotenhuis [4]	66 under 2 years old	53% success
Brockmeyer et al. [5]	98, all ages	49% overall success, no difference above/below 1.5 years
Burn et al. [6]	23 under 1 year old	39% overall success, success improves with age
Buxton et al. [8]	23 under 1 year old	30% success
Buxton et al. [7]	27 under 1 year old	30% success
Costa Val et al. [12]	53 under 2 years old	62% total success, aqueduct stenosis 86% success
Fritsch and Medhorn [14]	20 under 1 year old	60% success
Genitori et al. [15]	254, all ages	65% success under 1 year
Hopf et al. [20]	4 under 1 year old	100% failure
Hussain et al. [24]	13 (out of 102) under 2 years old	61% success
Javadpour et al. [25]	21 children under 1 year old	48% success
Jones et al. [26]	25 (out of 103) under 6 months old	32% success
Jones et al. [27]	11 (of 25) under 6 months old	9% success
Kamikawa et al. [30]	11 (of 88) under 1 year old	100% failure
Kim et al. [31]	6 (of 32) under 1 year old	33% success
Mori et al. [40]	12 under 1 year old	25% success
Osman-Farah et al. [43]	3 under 1 year old	66% success
Scarrow et al. [48]	13 (of 54) under 3 years old	46% success
Scavarda et al. [49]	4 premature babies	50% success
Wagner and Koch [57]	16 under 1 year old	31% success

assorted complications, providing no statistically significant results for this age group.

The varying standards for success and failure can be highlighted by comparing the following studies:

1. Mori et al. [40] obtained a 25% success rate for 12 children under 1 year of age and concluded that patients under 1 year of age are not candidates for ETV and V-P shunt is the treatment of choice. In those at the age of 1 year or older, ETV was recommended.
2. Buxton et al. [7] documented a success rate of 27% for 27 children under 1 year of age and concluded that ETV is the most appropriate initial treatment choice for infants, stating that although the majority fail, approximately one-third are spared the added morbidity and mortality of having a shunt. With such a low morbidity and zero mortality, the procedure has many benefits over shunting. They suggested that neuroendoscopic third ventriculostomy should be used where possible, rather than a shunt.
3. Kamikawa et al. [30] analyzed a group of 11 infants “mostly” under 1 year old. Their entire group eventually require shunting, yet they found statistically sig-

nificant advantages to initial treatment with an ETV attempt, despite the nonexistent “success rate,” concluding that even in failed patients under 1 year of age, ETV is safe and clinically effective as the first-line treatment of hydrocephalus in children.

Cinalli [9], in a comprehensive analysis of the options available for treatment of infants with obstructive hydrocephalus, summarized the position by stating that all the available data in the literature seem to show that third ventriculostomy offers at least as good an intellectual outcome as extracranial CSF shunts but also confirm the need for a controlled study.

Historical background leading to the organization of the study

In the last 5 years, as advocates of neuroendoscopy gathered to form the International Study Group on Neuroendoscopy (ISGNE), it became evident that beyond the enthusiasm to employ endoscopy as widely as possible, the lack of robust evidence on its efficacy was obvious. As a result, collab-

orative studies were undertaken, to try to move beyond the limited single institution studies, on these rare diseases. Gradually, a network of like-minded collaborating clinicians was established and managed to complete three retrospective studies:

- The first study (20 patients/4 centers) on the merits of repeat ETV was published in 2001 [51].
- The second study (101 patients/7 centers) on the merits of ETV following infection and/or hemorrhage was published in 2002 [50].
- Data collection for a third retrospective study on the safety and efficacy of endoscopic biopsies (International Neuroendoscopic Biopsy Study, INEBS) has been completed and is due to be published. Data on 280 patients have been collected from 13 centers worldwide during 2004.

A fourth international study on endoscopic treatment of pineal tumors has been designed already and will commence soon (Principal Investigator Prof. S. Oi).

The IIHS is a significantly more ambitious undertaking than any previous study, moving beyond retrospective data collection to a multicenter prospective randomized, controlled study. Its impact is anticipated to be far reaching:

- We hope to achieve statistically and clinically meaningful results to help resolve an issue for which the literature has thus far not been able to provide an objective answer. This is the only study to date that focuses on long-term developmental outcomes for hydrocephalic infants. As such, it will provide the means for better prenatal counseling when obstructive hydrocephalus is diagnosed in utero.
- This study will strengthen international collaboration in this field. The network of participating international investigators will provide the foundation and infrastructure for future international prospective studies.

Concept and rationale of the study

The proposed study represents a major departure from most published work on the value of neuroendoscopy in comparison to shunting in the treatment of hydrocephalus. Whereas most studies focus on the “survival” of the created stoma or implanted shunt and surgical complications of each procedure, this study focuses predominantly on the effect of both treatment types on neurodevelopmental outcome of these very young patients. Some neurosurgeons, skeptical on the value of ETV, believe that it may lead to an arrested form of hydrocephalus that compromises the developing brain. This belief is based on the observation that almost always, children who had ETV have ventricles considerably bigger in comparison to children who had shunting [54]. Still, no study has attempted to correlate the size of the ventricles to any developmental measurements,

so this belief has not been proven or refuted scientifically. Conversely, other neurosurgeons advocates of ETV are concerned with the long-term complications of shunting on the developing brain, especially the effects of shunt infections. This is based on the observed link between shunt infection and reduction of IQ and the measured memory deficits among shunted children [2, 45–47, 58]. Thus, they claim that ETV is a more “physiological” solution and therefore better for the infant’s brain. There has never been a direct controlled comparison of the two treatment types on their impact on intellectual development. For this reason, the primary outcome of the trial has been defined as the neurodevelopmental score at the age of 5 years. In that respect, it may well prove that one treatment type has considerably better neurodevelopmental outcome, but possibly higher complication rate. It will be up to the parents and the treating neurosurgeon in the future to choose one or the other treatment, knowing the full facts in detail.

In the same line of thought, it has been decided that other factors, such as complication rates, hospitalization time, need for repeat surgeries and imaging would be part of secondary measures. It will give us the opportunity to compare directly in controlled circumstances the complication rates between the two types of treatment, whereas, currently, no such information exists. Currently, when we are counseling our patients, we are quoting complication rates from different studies, always choosing subconsciously the most favorable ones, which unfortunately are not directly comparable, because at the very least they are not based on comparable patient populations.

It is clear that the study is not preoccupied with the success rate of ETV or the survival rate of the shunt in the traditional sense, but with the effect of either operative treatment on the developing brain, and as such, it is designed to provide a comprehensive assessment of the relevant relative benefits and risks. Essentially, it is the first randomized, controlled study on the long-term outcome of patients with infantile hydrocephalus due to aqueduct stenosis.

Due to the lack of clear superiority for either surgical technique, it became obvious that randomization in shunt or ETV group, in the clearly defined population of infants under 2 years of age with obstructive hydrocephalus due to pure aqueduct stenosis, is not only ethical but also a duty for all involved in the management of such patients. Nevertheless, families who are presented with both options in a nonbiased way and elect to choose one, possibly on the basis on information that they may have already gathered on their own, may also be included in the study. This does not violate the statistical validity of the study and is designed in the model of a comprehensive cohort design [42].

Neurodevelopmental aspects

Neurodevelopmental assessment of the recruited patients is a key component of the study and, in view of the very

young age of the patients, poses certain challenges that needed to be overcome. Hydrocephalus is known to be associated with memory and behavior deficits, and shunt complications are known to influence these functions [13, 22, 23, 44–46, 58, 60]. Nevertheless, all studies that have explored such issues have limited themselves to testing of patients at older ages, well after treatment has been completed, and effectively, they represent incidence studies for that particular problem. This study aims to provide prospective data on preoperative and postoperative testing at fixed ages. By obtaining tests and subsequent scores at predetermined ages, rather than at fixed intervals after surgery, we have streamlined the data that will result and make them comparable, from patient to patient and between the two treatment groups, as well as to normal age matched scores.

For preoperative testing, we have adapted the Denver Developmental Screening Test questionnaire for each month of life, as in these first 24 months of life rapid developmental changes which are normally expected and observed. Postoperative testing for ages of 12, 24, and 36 months is an adaptation of the Denver Developmental Screening Test. For age of 5 and (optional) 7 years, we have employed a combination of the Health Utilities Index (HUI) [21], the Hydrocephalus Outcome Questionnaire (HOQ) [33], and, as an option, the standard Wechsler test. The objective is to have a neurodevelopmental score at each stage, which will be used for statistical comparisons.

Surgical aspects

The study assumes that the participating surgeons fully endorse the rational and the concept of randomization. Hence, the surgeon is expected to explain to the parents the pros and cons of the two surgical methods without compassion and demonstrate the reason behind randomization. While the study does not dictate the use of any particular type of shunt in the shunted group or any particular endoscope or technique in the ETV group, we have defined a minimum of experience from the surgeon of at least ten neuroendoscopic procedures per year and a minimum of five ETV procedures in infants, as a criterion to be accepted to join the study group. We have not set a minimum level of shunt operations, as they are far more common. Hence, all neurosurgeons who have declared an interest to join the study function in environments of established pediatric neurosurgery departments, attracting high enough numbers of patients, sufficient to recruit the rare subgroup of infants with pure aqueduct stenosis. The type of shunt is not considered likely to influence the neurodevelopmental outcome significantly at 5 years of age, and for this reason, we have not controlled it. Moreover, demanding that only one type of shunt is used in the study patients can be viewed as a commercial endorsement of one particular product, which can only lead to credibility and compliance problems, as most neurosurgeons have very fixed views on

shunts. The type of endoscope and the technique employed to perforate the floor of the third ventricle are equally not considered likely to influence the neurodevelopmental outcome at 5 years of age. Most endoscopes are of similar caliber, and all instruments used to perforate the floor of the third ventricle cause the same degree of “damage”. Nevertheless, information on such technical issues will be collected and analyzed as part of the secondary analyses.

Patient inclusion criteria extended to previously untreated children presenting under the age of 24 months, of full-term pregnancy (>36 weeks), with triventricular hydrocephalus due to pure aqueduct stenosis diagnosed on MR scan. We strictly excluded children with spina bifida of any variety, prematurity, neonatal IVH, perinatal asphyxia, other congenital malformations such as Dandy-Walker syndrome or severe anatomical dysmorphic features (e.g., heterotopias, corpus callosum agenesis, large cysts) and central nervous system tumor.

Statistical considerations

Sample size

The sample size estimate is based on the ability to detect a statistically significant difference between the treatment groups for the primary outcome: the HUI score at 5 years of age. The following estimations and assumptions have been made:

- The mean HUI score for the control (CSF shunt) group will be approximately 0.77 and the standard deviation will be 0.20, based on our previous work [32, 33].
- The magnitude of a clinically meaningful difference in the primary outcome is judged to be an approximately 0.10 increase in the HUI score in the ETV cohort (i.e., a mean utility score of 0.87). This is also based on previous work (Kulkarni 2005 unpublished data).
- α value=0.05 (two-sided) and β =0.20 (80% power).

Based on the preceding set of baseline assumptions and using the independent-samples *t* test, it is estimated that at least 64 patients per group are required to reach statistical significance. If we conservatively allow for an approximate 30% loss to follow-up, the sample size estimate can be adjusted to *91 patients per group*.

Primary analysis

The primary analysis will be performed on the HUI utility scores obtained at 5 years of age. The primary analysis will be confined to the randomized cohort only and consist of a simple independent-samples *t* test. An adjusted, multi-variable analysis of covariance will also be performed in which the following variables will be included: randomized intervention (ETV or CSF shunt), age at surgery (in weeks),

gender, preoperative ventricular size, and baseline neurodevelopmental level.

Secondary analyses

Several secondary analyses will be performed, including survival analysis of time to failure of the initial intervention (to be performed 2 years after closure of enrollment), differences in outcome as measured by the HOQ, and comparison of perioperative complications between ETV and CSF shunt groups. These analyses will use data from both the randomized and nonrandomized cohort, separately and in combination.

All primary and secondary analyses for the randomized group will be done on an intention-to-treat basis, whereby patient outcome will be analyzed according to the group to which they were originally assigned.

Interim analysis

One interim analysis of survival, using Fisher's exact test, is planned after 50% of the anticipated patient recruitment has completed an initial 9-month period of follow-up in the study. The results will be presented (with treatment allocation blinded) to the monitoring committee. The monitoring committee will then decide whether to continue with the study or stop. If one treatment achieves a statistically significant greater initial success rate at a p value below 0.001, then the monitoring committee will have instructions to recommend stopping the trial. The monitoring committee will not be restricted to an imbalance in the success rate alone. It may also consider other factors, including excessive adverse events.

Administration

For the first time in a neurosurgical prospective randomized trial, we are seeking to administer the entire study using internet technology. Traditionally, trials are administered through paper forms, which can result in a significant time delay between patient recruitment, patient randomization, data collection, and data compilation at the coordinating center. This often leads to collection of inaccurate data, as in most trials, though prospective, the various patient information forms are filled after the event, and not always completely. Use of online internet technology for recruitment, randomization, and data collection ensures contemporaneous data entry and improved accuracy, as the computer technology can force the user to answer certain key questions before proceeding to the next step. In addition, it allows the steering committee to have a real time view of the patients recruited and their eligibility and provide appropriate guidance to the participating centers.

The way forward

The IIHS has been endorsed with great enthusiasm by a great number of neurosurgeons, and as of April 2005, at least 25 centers have committed themselves to participate, and the first few patients have been recruited. It is expected that the study will provide the desired answers and create a close web of collaborating surgeons, who in the future will pursue even more ambitious projects. At the time of evidence-based medicine and ever declining funding for research, a contradiction of trends in its own right, it is refreshing to see surgeons striving to pursue their questions scientifically.

References

1. Abstracts of the Second World Conference of the International Study Group on Neuroendoscopy (ISGNE) (2003) Castel dell' Ovo, Naples, Italy, 11–13 September 2003. *Childs Nerv Syst* 19:687–709
2. Ammirati M, Raimondi A (1987) Cerebrospinal fluid shunt infections in children. A study on the relationship between the etiology of hydrocephalus, age at the time of shunt placement, and infection rate. *Childs Nerv Syst* 3:106–109
3. Baskin JJ, Manwaring KH, Rekate HL (1998) Ventricular shunt removal: the ultimate treatment of the slit ventricle syndrome. *J Neurosurg* 88:478–484
4. Beems T, Grotenhuis JA (2002) Is the success rate of endoscopic third ventriculostomy age-dependent? An analysis of the results of endoscopic third ventriculostomy in young children. *Childs Nerv Syst* 18:605–608
5. Brockmeyer D, Abtin K, Carey L, Walker ML (1998) Endoscopic third ventriculostomy: an outcome analysis. *Pediatr Neurosurg* 28:236–240
6. Buxton N, Saxena A, Tyagi A, Chumas PD (2003) Endoscopic third ventriculostomy in children during the first year of life. *Childs Nerv Syst* 19:618–619
7. Buxton N, Macarthur D, Mallucci C, Punt J, Vloeberghs M (1998a) Neuroendoscopic third ventriculostomy in patients less than 1 year old. *Pediatr Neurosurg* 29:73–76
8. Buxton N, Macarthur D, Mallucci C, Punt J, Vloeberghs M (1998b) Neuroendoscopy in the premature population. *Childs Nerv Syst* 14:649–652
9. Cinalli G (1999) Alternatives to shunting. *Childs Nerv Syst* 15:718–731
10. Cinalli G, Sainte-Rose C, Chumas P, Zerah M, Brunelle F, Lot G, Pierre Kahn A, Renier D (1999) Failure of third ventriculostomy in the treatment of aqueductal stenosis in children. *J Neurosurg* 90:448–454
11. Cinalli G, Salazar C, Mallucci C, Yada JZ, Zerah M, Sainte-Rose C (1998) The role of endoscopic third ventriculostomy in the management of shunt malfunction. *Neurosurgery* 43:1323–1327; discussion 1327–1329

12. Costa Val JA, Noci TR, Lara A, Herval LM, Serrano P (2003) Endoscopic third ventriculostomy in children under 2 years old: experience of a neuropsychiatric service in Brazil. *Childs Nerv Syst* 19:688
13. Dennis M, Barnes MA (1993) Oral discourse after early-onset hydrocephalus: linguistic ambiguity, figurative language, speech acts, and script-based inferences. *J Pediatr Psychol* 18:639–652
14. Fritsch MJ, Medhorm HM (2003) Indication and controversies for endoscopic third ventriculostomy in children. *Childs Nerv Syst* 19:706–707
15. Genitori L, Peretta P, Mussa F, Giordano F (2003) Endoscopic third ventriculostomy in children: are age and etiology of hydrocephalus predictive factors influencing the outcome in primary and secondary treated patients? A series of 254 patients and 276 procedures. *Childs Nerv Syst* 19:618
16. Goumnerova LC, Frim DM (1997) Treatment of hydrocephalus with third ventriculocisternostomy: outcome and CSF flow patterns. *Pediatr Neurosurg* 27:149–152
17. Grotenhuis JA, Beems T (1999) The role of endoscopic third ventriculostomy in the treatment of hydrocephalus associated with myelomeningocele. *Minim Invasive Neurosurg* 42:161–162
18. Hirsch JF, Pierre-Kahn A, Renier D, Sainte-Rose C, Hoppe-Hirsch E (1984) The Dandy–Walker malformation. A review of 40 cases. *J Neurosurg* 61:515–522
19. Hoffman HJ, Harwood-Nash D, Gilday DL (1980) Percutaneous third ventriculostomy in the management of noncommunicating hydrocephalus. *Neurosurgery* 7:313–321
20. Hopf NJ, Grunert P, Fries G, Resch KD, Perneczky A (1999) Endoscopic third ventriculostomy: outcome analysis of 100 consecutive procedures. *Neurosurgery* 44:795–804; discussion 804–796
21. Horsman J, Furlong W, Feeny D, Torrance G (2003) The Health Utilities Index (HUI): concepts, measurement properties, and applications. *Health Qual Life Outcomes* 16:54
22. Hurley AD, Bell S (1994) Educational and vocational outcome of adults with spina bifida in relationship to neuropsychological testing. *Eur J Pediatr Surg* 4(Suppl 1):17–18
23. Hurley AD, Laatsch LK, Dorman C (1983) Comparison of spina bifida, hydrocephalic patients and matched controls on neuropsychological tests. *Z Kinderchir* 38(Suppl 2):116–118
24. Husain M, Jha D, Vatsal DK, Thaman D, Gupta A, Husain N, Gupta RK (2003) Neuro-endoscopic surgery—experience and outcome analysis of 102 consecutive procedures in a busy neurosurgical centre of India. *Acta Neurochir (Wien)* 145:369–376
25. Javadpour M, Mallucci C, Brodbelt A, Golash A, May P (2001) The impact of endoscopic third ventriculostomy on the management of newly diagnosed hydrocephalus in infants. *Pediatr Neurosurg* 35:131–135
26. Jones RF, Kwok BC, Stening WA, Vonau M (1994) Neuroendoscopic third ventriculostomy. A practical alternative to extracranial shunts in non-communicating hydrocephalus. *Acta Neurochir Suppl (Wien)* 61:79–83
27. Jones RF, Kwok BC, Stening WA, Vonau M (1996) Third ventriculostomy for hydrocephalus associated with spinal dysraphism: indications and contraindications. *Eur J Pediatr Surg* 6 (Suppl 1):5–6
28. Jones RF, Stening WA, Brydon M (1990) Endoscopic third ventriculostomy. *Neurosurgery* 26:86–91; discussion 91–82
29. Jones RF, Stening WA, Kwok BC, Sands TM (1993) Third ventriculostomy for shunt infections in children. *Neurosurgery* 32:855–859; discussion 860
30. Kamikawa S, Inui A, Kobayashi N, Kuwamura K, Kasuga M, Yamadori T, Tamaki N (2001) Endoscopic treatment of hydrocephalus in children: a controlled study using newly developed Yamadori-type ventriculoscopes. *Minim Invasive Neurosurg* 44:25–30
31. Kim SK, Wang KC, Cho BK (2000) Surgical outcome of pediatric hydrocephalus treated by endoscopic III ventriculostomy: prognostic factors and interpretation of postoperative neuroimaging. *Childs Nerv Syst* 16(3):161–169
32. Kulkarni AV, Drake JM, Rabin D, Dirks PB, Humphreys RP, Drake JT (2004) Measuring the health status of children with hydrocephalus using a new outcome measure. *J Neurosurg Pediatr* 101:141–146
33. Kulkarni AV, Rabin D, Drake JM (2004) An instrument to measure the health status of children with hydrocephalus: the Hydrocephalus Outcome Questionnaire. *J Neurosurg Pediatr* 101:134–140
34. Macarthur DC, Buxton N, Vloeberghs M, Punt J (2001) The effectiveness of neuroendoscopic interventions in children with brain tumours. *Childs Nerv Syst* 17:589–594
35. Mallucci C, Vloeberghs M, Punt J (1997) Neuroendoscopic third ventriculostomy: the first line treatment for blocked ventriculo-peritoneal shunts? *Childs Nerv Syst* 13:498
36. Mallucci C, Vloeberghs M, Punt J (1997) Should shunts be revised when neuroendoscopic third ventriculostomy is available? *Br J Neurosurg* 11:473
37. Meier U, Zeilinger FS, Schonherr B (2000) Endoscopic ventriculostomy versus shunt operation in normal pressure hydrocephalus: diagnostics and indication. *Acta Neurochir Suppl (Wien)* 76:563–566
38. Meier U, Zeilinger FS, Schonherr B (2000) Endoscopic ventriculostomy versus shunt operation in normal pressure hydrocephalus: diagnostics and indication. *Minim Invasive Neurosurg* 43:87–90
39. Mitchell P, Mathew B (1999) Third ventriculostomy in normal pressure hydrocephalus. *Br J Neurosurg* 13:382–385
40. Mori H, Nishiyama K, Tanaka R (2003) Endoscopic third ventriculostomy for pediatric hydrocephalic patients: discussion of the indication and strategy for shunt removal. *Childs Nerv Syst* 19:618
41. Murshid WR (2000) Endoscopic third ventriculostomy: towards more indications for the treatment of non-communicating hydrocephalus. *Minim Invasive Neurosurg* 43:75–82
42. Olschewski M, Schumacher M, Davis KB (1992) Analysis of randomized and nonrandomized patients in clinical trials using the comprehensive cohort follow-up study design. *Control Clin Trials* 13:226–239
43. Osman-Farah J, Javadpour M, Buxton N, May P, Mallucci C (2003) Endoscopic ventricular fenestration and ETV for the treatment of multicompartamental neonatal hydrocephalus. *Childs Nerv Syst* 19:702–703
44. Pelegrin Valero C, Tirapu Ustarroz J, Landa Gonzalez N (2001) Neuropsychological deficits in hydrocephalus associated spina bifida. *Rev Neurol* 32:489–497
45. Pople IK, Bayston R, Hayward RD (1992) Infection of cerebrospinal fluid shunts in infants: a study of etiological factors. *J Neurosurg* 77:29–36

46. Renier D, Lacombe J, Pierre-Kahn A, Sainte-Rose C, Hirsch JF (1984) Factors causing acute shunt infection. Computer analysis of 1174 operations. *J Neurosurg* 61:1072–1078
47. Sainte-Rose C, Piatt JH, Renier D, Pierre-Kahn A, Hirsch JF, Hoffman HJ, Humphreys RP, Hendrick EB (1992) Mechanical complications in shunts. *Pediatr Neurosurg* 17:2–9
48. Scarrow AM, Levy EI, Pascucci L, Albright AL (2000) Outcome analysis of endoscopic III ventriculostomy. *Childs Nerv Syst* 16:442–444
49. Scavarda D, Bednarek N, Litre F, Koch C, Lena G, Morville P, Rousseaux P (2003) Acquired aqueductal stenosis in preterm infants: an indication for neuroendoscopic third ventriculostomy. *Childs Nerv Syst* 19:756–759
50. Siomin V, Cinalli G, Grotenhuis A, Golash A, Oi S, Kothbauer K, Weiner H, Roth J, Beni-Adani L, Pierre-Kahn A, Takahashi Y, Mallucci C, Abbott R, Wisoff J, Constantini S (2002) Endoscopic third ventriculostomy in patients with cerebrospinal fluid infection and/or hemorrhage. *J Neurosurg* 97:519–524
51. Siomin V, Weiner H, Wisoff J, Cinalli G, Pierre-Kahn A, Saint-Rose C, Abbott R, Elran H, Beni-Adani L, Ouaknine G, Constantini S (2001) Repeat endoscopic third ventriculostomy: is it worth trying? *Childs Nerv Syst* 17:551–555
52. Smyth MD, Tubbs RS, Wellons JC III, Oakes WJ, Blount JP, Grabb PA (2003) Endoscopic third ventriculostomy for hydrocephalus secondary to central nervous system infection or intraventricular hemorrhage in children. *Pediatr Neurosurg* 39:258–263
53. Snow JH, Prince M, Souheaver G, Ashcraft E, Stefans V, Edmonds J (1994) Neuropsychological patterns of adolescents and young adults with spina bifida. *Arch Clin Neuropsychol* 9:277–287
54. St George E, Natarajan K, Sgouros S (2004) Changes in the ventricular volume in hydrocephalic children following successful endoscopic third ventriculostomy. *Childs Nerv Syst* 20:834–838
55. Teo C, Jones R (1996) Management of hydrocephalus by endoscopic third ventriculostomy in patients with myelomeningocele. *Pediatr Neurosurg* 25:57–63
56. Teo C, Rahman S, Boop FA, Cherny B (1996) Complications of endoscopic neurosurgery. *Childs Nerv Syst* 12:248–253
57. Wagner W, Koch D (2003) Success or failure of endoscopic third ventriculostomy in young infants: is there a correlation with age in patients up to 12 months old? *Childs Nerv Syst* 19:618
58. Walters BC, Hoffman HJ, Hendrick EB, Humphreys RP (1984) Cerebrospinal fluid shunt infection. Influences on initial management and subsequent outcome. *J Neurosurg* 60:1014–1021
59. Wellons JC III, Tubbs RS, Banks JT, Grabb B, Blount JP, Oakes WJ, Grabb PA (2002) Long-term control of hydrocephalus via endoscopic third ventriculostomy in children with tectal plate gliomas. *Neurosurgery* 51:63–67; discussion 67–68
60. Wills KE (1993) Neuropsychological functioning in children with spina bifida and/or hydrocephalus. *J Clin Child Psychol* 22:247–265